

**Research Article**

Persistent Pulmonary Abnormalities Following Hospitalization for Moderate or Severe COVID-19: Unmasking the Risk Factors

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Abstract

Objectives: To assess the presence and potential risk factors of persistent lung abnormalities on follow-up CT scans after hospitalization for COVID-19. While initial CT scans of COVID-19 patients have been studied extensively, knowledge about long-term lung abnormalities remains limited. **Material and methods:** A prospective observational study was conducted. 337 adults hospitalized for moderate or severe COVID-19 were included. Two radiologists evaluated the initial and follow-up chest CT scans three months after discharge for the presence of COVID-19 associated abnormalities: ground glass opacities, crazy paving, consolidations, reticulations, vasodilatation, and bronchiectasis. Patients were divided into two groups: those with fibrotic-like changes on follow-up CT scans (n=193) and those without (n=144). Data regarding patient characteristics, medical history, hospitalization parameters and clinical symptoms of patients were included in the statistical analysis. **Results:** Patients with fibrotic-like changes on CT were significantly older, had higher CT severity score at admission and demonstrated a higher rate of ICU admission during hospitalization compared to those without these changes. Inflammatory markers were statistically higher in patients with fibrotic-like changes. A statistically significant difference was observed in crazy paving on initial scans, with a higher proportion (53.16%, 101 patients) in the fibrotic group compared to the non-fibrotic group (11.11%, 4 patients). **Conclusion:** This study demonstrates that older age, severe initial illness requiring ICU admission and elevated inflammatory markers are important risk factors for developing fibrotic changes on follow-up CT scans after hospitalization for COVID-19.

Keywords: COVID-19; CT; Chest; Infection; Intensive Care Unit.

Introduction

The emergence of Severe Acute Respiratory Syndrome Coronavirus Type 2 (SARS-CoV-2) in late 2019, resulting in Coronavirus Disease 2019 (COVID-19), had a substantial global impact.

Extensive research efforts have been made and while a significant number of studies focused on the acute phase of the disease, a noteworthy gap remains in our knowledge of the post-acute and late phases. Existing data on later stages of the disease are often heterogeneous and require further investigation. The sequelae of COVID-19 are multi-systemic with pulmonary manifestations being the most frequent [1]. The aim of this study is to assess the

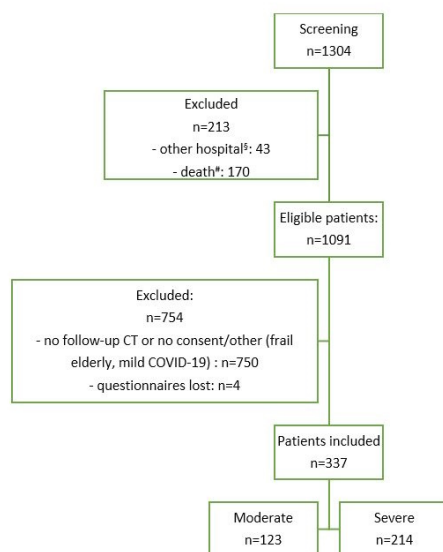
presence and potential risk factors of persistent lung abnormalities after hospitalization on follow-up CT three months after discharge. Understanding these persistent abnormalities on chest CT is vital, as hospitalized patients tend to experience more severe outcomes and a greater burden of long-term health issues.

Material and methods

Study participants

To conduct a prospective observational follow-up study, adult patients (>18 years old) admitted to University Hospital Ghent between 01/03/2020 and 15/02/2021 were approached for study participation. Those who met the inclusion criteria were included as outlined in the flow chart (Figure 1). Inclusion criteria comprised: confirmed SARS-CoV-2 infection through nasopharyngeal swab RT-PCR testing or bronchoalveolar lavage fluid, hospitalization for moderate or severe COVID-19 (according to the WHO-CPS criteria [2] for moderate or severe COVID-19), and completion of post-discharge follow-up visit, including a CT scan. Written informed consent was obtained from all study participants. The study protocol received approval from the local ethics committee at University Hospital Ghent (BC-07831/BC-10247).

Flow chart of inclusion of COVID-19 patients



§: follow-up at referring hospital or discharge to care home; #: death prior to discharge; +: patients who did not attend or refused follow-up or refused consent for enrolment

Figure 1: Flow chart of inclusion of COVID-19 patients.

Image analysis

Chest CT scans including High-Resolution Computed Tomography (HRCT) (Somatom Definition Edge, Siemens Healthineers, Erlangen, Germany) were acquired at three months following hospital discharge for COVID-19. All scans were performed with patients in the supine position during end-inspiration breath-hold.

Intravenous contrast material administration was not used. Two radiologists (J.K. and L.M. with respectively five and twelve years of experience) evaluated the CT scans in consensus for the presence of the following potentially COVID-19 associated abnormalities: Ground Glass Opacities (GGO), crazy paving, consolidations, reticulations, vasodilatation, and bronchiectasis (Table 1, Figure 2, 3, 4). When available, follow-up CT scans were compared to initial admission chest CT scans (available in 226 patients), as outlined in Supplemental Table 1. Less frequent findings or those potentially unrelated to COVID-19 were documented verbally within the “other” category. Ultimately, a CT severity score (CTSS, 0-25) based on the Pan et al. scoring system was assigned to each initial and follow-up scan, reflecting the extent of lung involvement [3,4] (Table 2). CT findings were classified based on their potential link to fibrosis. Reticulations and bronchiectasis, commonly seen in fibrotic lungs, were categorized as fibrosis-like. Conversely, crazy paving, consolidations, and vasodilatation were categorized as non-fibrosis-like, potentially reflecting continued acute inflammation.

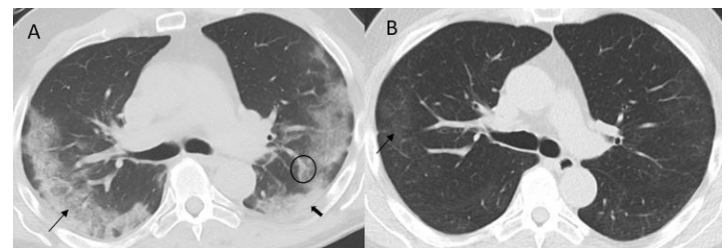


Figure 2: 69-year-old man hospitalized for COVID-19 pneumonia. A) Baseline axial CT showing consolidations (thick arrow), vasodilatation (circle) and ground glass opacifications (thin arrow) with peripheral distribution. B) 3-month follow-up axial CT demonstrating discrete residual ground glass opacifications (thin arrow).

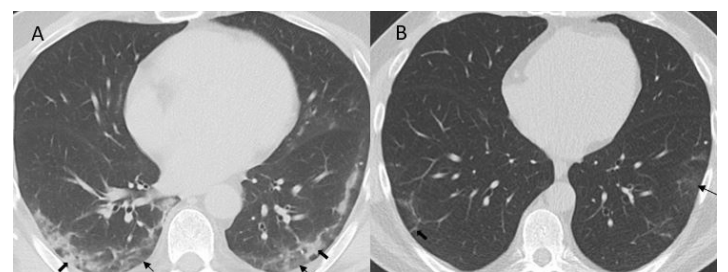


Figure 3: 60-year-old man hospitalized for COVID-19 pneumonia. A) Baseline axial CT showing bilateral band-shaped consolidation (thick arrows) and ground glass opacities (thin arrows) with peripheral distribution. B) 3-month follow-up axial CT demonstrating the complete resolution of consolidation, with residual discrete bilateral subpleural reticulations (thick arrow) and discrete ground glass opacifications (thin arrow).

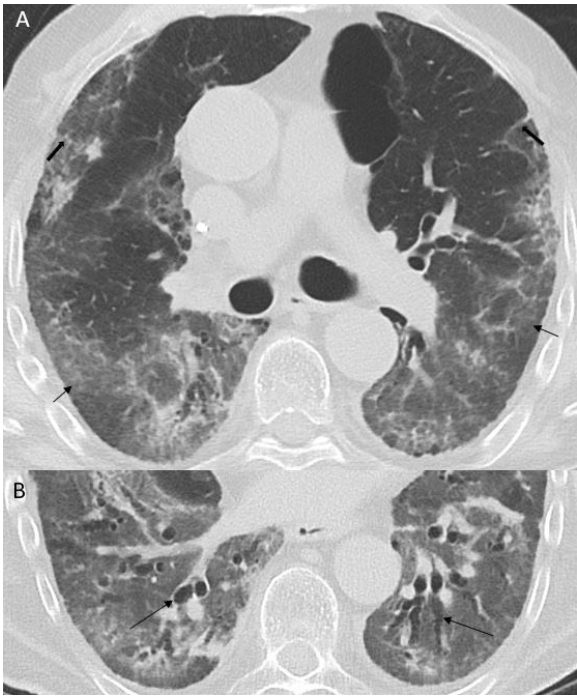


Figure 4: 73-year-old man after COVID pneumonia.

A) Axial follow-up CT showed long fibrosis with reticulations (thick arrows), ground glass opacifications (short thin arrows) and architectural distorsion. B) These changes were most pronounced in the lower lobes of the lungs, where they led to the traction bronchiectasis (long thin arrows).

All			Fibrotic		Non-fibrotic		p-value
CT available	226		190		36		
CT severity score	12,16 (0 -23)		12,41 (3- 23)		10,92 (0 - 21)		0.025
Anomalies							
Normal findings	0	0.00%	0	0.00%	0	0.00%	1
GGO	214	94.69%	178	93.68%	36	100.00%	0.061
Crazy paving	105	46.46%	101	53.16%	4	11.11%	<0,001
Consolidation	131	57.96%	107	56.32%	24	66.67%	0.125
Reticulation	179	79.20%	179	94.21%	0	0.00%	<0,001
Vasodilation	70	30.97%	60	31.58%	10	27.78%	0.075
Bronchiectasis	61	26.99%	61	32.11%	0	0.00%	<0,001
GGO=ground glass opacification							

Supplementary Table 1: Summary of radiological findings on CT scans at admission to the hospital.

CT available	337		193		144		-
CT severity score	4,3175 (0 - 20)		6,3523 (0 - 19)		1,5903 (0 - 20)		<0,001
Anomalies							
Normal findings	99	29.38%	0	0.00%	99	68.75%	<0,001
GGO	180	53.41%	135	69.95%	45	31.25%	<0,001
Crazy paving	11	3.26%	11	5.70%	0	0.00%	0.002
Consolidation	6	1.78%	2	1.04%	4	2.78%	0.116
Reticulation	186	55.19%	186	96.37%	0	0.00%	<0,001
Vasodilation	0	0.00%	0	0.00%	0	0.00%	1
Bronchiectasis	58	17.21%	58	30.05%	0	0.00%	<0,001
GGO = ground glass opacification							

Table 1: Summary of radiological findings on CT scans at 3 months follow-up.

	N		n	p-value
Average CT SS at admission	12.18777		226	
Average CT SS at 3 months follow-up	4.922747		226	
Average CT SS at 3 months follow up (all patients)	4.317507		337	
% of patients with fibrotic-like changes on CT at admission	84.07%	190	226	<0,001**
CT at 3 months follow-up				
% of patients with fibrotic changes	57.27%	193	337	
% of patients with other changes	54.01%	182	337	
% of patients with both types	40.65%	137	337	
% of patients with no changes	29.38%	99	337	
% of patients with any changes	70.62%	238	337	<0,001*
* t-test of statistical difference between the fractions of people having any changes on follow up at 3 months CT scan in comparison to patients without radiological changes; ** t-test of statistical difference between the fraction of people having fibrotic changes during and after hospitalization.				

Table 2: Basic characteristics of executed CT scans.

Statistical analysis

Data about image analysis and patient characteristics (Table 3 and supplemental Table 2), hospitalization parameters (Table 4), medical history (supplemental Table 3), and clinical symptoms of patients (supplemental material Table 4) were collected. The data were analyzed by IBM SPSS statistics (version 29.0, BM Corp., Armonk, NY, USA). The qualitative data were described as number and percentage and analyzed by using the variable independence *Chi square test*. Quantitative data were described as

mean, standard deviation, and range; t-test and normal distribution mean difference test were used to compare normally and not normally distributed quantitative data, respectively. Normality for continuous variables was checked using the Shapiro-Wilks test and if their normal distribution was not confirmed, variables were expressed with median and interquartile range. A one-sided p-value of <0.05 was considered statistically significant. Logistic regression models were employed to examine the relationships between binary (dependent) and numeric (independent) variables.

The significance of individual regression coefficients within the model was assessed using Wald tests (not t-tests). Model performance was evaluated using two key metrics: Accuracy Ratio and Likelihood Ratio Test. A significant likelihood ratio test (p-value <0.05) indicates that the model with all predictors provides a statistically better fit to the data compared to the intercept-only model.

	Studied group n = 337				test	p-value	
	Non-fibrotic n=144			Fibrotic n=193			
Age	mean	54,51+-12,25		63,53+-10,83		6.99	<0,001
	range	21-81		33-91		test t	
Gender	male	90	62.50%	129	66,84%	0.68	0.409
	female	54	37.50%	64	33,16%	test chi^2	
Ethnicity	white	126	87,50%	170	88,08%	0.03	0.87
	other	18	12,50%	23	11,92%	test chi^2	
CTSS	mean	1,59+-3,21		6,35+-3,96		11.83	<0,001
	range	0-20		0-19		test t	
Smoking	Smokers	70	48.61%	91	47.15%	0.07	0.791
	No smokers	74	51.39%	102	52.85%	test chi^2	
BMI	mean	29,97+-5,71		29,64+-4,86		0.54	0.294
	range	18,40-53,92		17,63-45,67		test t	
CT SS = computed tomography severity scale; BMI= Body Mass Index							

Table 3: Baseline characteristics of patients with and without fibrotic-like changes.

		Studied Group N=337
Age (years)	Mean	60
	Range	21-91
Gender	Female	115 (34%)
	Male	222 (66%)
Ethnicity	White	297 (88,1%)
	Arab	31 (9,2%)
	Black	6 (1,8%)
	Asian	1 (0,3%)
	Turk	1 (0,3%)
	Hispanic	1 (0,3%)
BMI (kg/m²)	Mean	29,8
	Range	17,6-53,9
Smoking	Smokers	161 (48%)
	Non-smokers	176 (52%)

Comorbidities	Arterial hypertension	143 (42%)
	Hyperlipidemia	91 (27%)
	Diabetes	76 (23%)
	Ischemic heart disease	38 (11%)
	Heart failure	16 (5%)
	Lung disease:	
	Asthma	26 (8%)
	COPD	11 (3%)
	ILD	8 (2%)

Supplementary Table 2: Baseline characteristics of the studied patients.

	Studied group: n = 337					test	p-value
		Non-fibrotic n=144		Fibrotic n=193			
ICU stay	yes	29	20.14%	82	42.49%	18.65	<0,001
	no	115	79.86%	111	57.51%	test chi^2	
Rehospitalization	yes	3	2.08%	5	2.59%	0.09	0.762
	no	141	97.92%	188	97.41%	test chi^2	
Corticosteroids	yes	72	50.00%	138	71.50%	16.24	<0,001
	no	72	50.00%	55	28.50%	test chi^2	
O ₂	yes	133	92.36%	186	96.37%	2.63	0.105
	no	11	7.64%	7	3.63%	test chi^2	
Peak CRP	mean	124,66+-85,11		165,58+-109,49		3.78	<0,001
	range	3-399		1-562		test t	
Ferritin	mean	144,48+-131,25		173,64+-172,31		1.57	0.059
	range	6-820		6-1154		test t	

ICU=Intensive Care Unit; O₂=oxygen therapy; CRP=C-reactive protein

Table 4: Hospitalization parameters of patients with and without fibrotic-like changes.

Studied group: n=337						test	p-value
		Non-fibrotic n=144		Fibrotic n=193			
IHD	present	10	6.94%	28	14.51%	4.72	0.03
	absent	134	93.06%	165	85.49%	test chi^2	
VHD	present	1	0.69%	10	5.18%	5.23	0.022
	absent	143	99.31%	183	94.82%	test chi^2	
Solid organ Tx	present	7	4.86%	16	8.29%	1.52	0.217
	absent	137	95.14%	177	91.71%	test chi^2	
Heart failure	present	4	2.78%	12	6.22%	2.16	0.142
	absent	140	97.22%	181	93.78%	test chi^2	
Oncological history	present	13	9.03%	33	17.10%	4.56	0.033
	absent	131	90.97%	160	82.90%	test chi^2	

IHD=ischemic heart disease; VHD=valvular heart disease; Tx=transplant

Supplementary Table 3: Medical history of patients with and without fibrotic-like changes.

Studied group: n=337						test	p-value
		Non-fibrotic n=144		Fibrotic n=193			
Shortness of breath	present	78	54.17%	108	55.96%	0.11	0.744
	absent	66	45.83%	85	44.04%	test chi^2	
Cough	present	24	16.67%	21	10.88%	2.39	0.122
	absent	120	83.33%	172	89.12%	test chi^2	
Fatigue	present	84	58.33%	96	49.74%	2.44	0.118
	absent	60	41.67%	97	50.26%	test chi^2	
Lung auscultation	normal	130	90.28%	158	81.87%	4.7	0.03
	not normal	14	9.72%	35	18.13%	test chi^2	

Supplementary Table 4: Clinical follow-up of patients with and without fibrotic-like changes.

Results

Study participants

Of the 1304 patients hospitalized during the study period, 1091 met the inclusion criteria and were invited for a follow-up visit three months after discharge. A subgroup of 335 patients who underwent post-discharge CT scans were included in further analyses (Figure 1). The study enrolled 222 males and 115 females, resulting in a male-to-female ratio of 1.92:1. The patients' ages ranged from 21 to 91 years old, with a median age of 60 years.

Initial CT vs. follow-up CT

Out of the total study population, 226 patients (67,06%) underwent CT scan on admission (Supplemental Table 1). While the prevalence of fibrotic-like changes remained substantial on the follow-up CT scans (57.27%), it was statistically significantly lower ($p<0.001$) compared to the initial CT scans (84.07%). GGO was the most frequent finding, observed in 214 scans (94.69%) followed by reticulations (79,20%) and consolidations (57,96%), identified in 179 and 131 scans, respectively. There was no CT scan detected without any abnormalities. The most common lung changes on follow-up CT scans differed from the initial scans. Reticulation emerged as the leading abnormality, observed in over half of the patients (186 patients, 55.19%). GGO remained frequent (180 patients, 53.41%), followed by bronchiectasis (58 patients, 17.21%). Crazy paving, previously observed in a substantial portion of patients, showed significant resolution, with only 11 patients (3.26%) still exhibiting it. Vasodilatation, which was observed in 70 patients on initial CT scans, was no longer detectable on follow-up scans.

Fibrotic and non-fibrotic group on follow-up CT

A significantly higher proportion ($p<0.001$) of patients exhibited residual abnormalities on their follow-up CT scans (70.62%) compared to those with no detectable changes (29.38%) (Table 1). The study divided patients into two groups based on their follow-up CT scans, patients with fibrotic-like changes (57.27%) such as reticulations or bronchiectasis and those with other abnormalities or no residual findings (42.73%). Interestingly, a subset of patients (40.65%) exhibited both types of lung abnormalities on follow-up CT scans. GGO and consolidations did not show a significant difference in prevalence between the groups. On the other hand, crazy paving demonstrated statistical significance, as it was observed in over half (53.16%, 101 patients) of the fibrotic-like group compared to only 11.11% (4 patients) in the non-fibrotic group. Patients with fibrotic-like changes were considerably older on average, with a mean age of 63.53 years, compared to 54.51 years in the group without such changes (Table 3). Gender, ethnicity, and smoking history did not have impact on the development of fibrotic-like changes. Neither group had a significantly higher average Body Mass Index (BMI) compared to the other. Patients who had in their medical history ischemic heart disease, valvular heart disease or oncological history were more prone to develop fibrotic-like changes (supplemental table 3). Patients with fibrotic-like changes displayed a significantly higher rate of Intensive Care Unit (ICU) admission (42.49%) compared to those without these changes (20.14%) (Table 4). The mean peak CRP level reached 165.58 in the fibrotic-like group compared to 124.66 in the non-fibrotic group. Similarly, ferritin levels were significantly higher in the fibrotic-like group (mean 173.64) compared to the non-fibrotic group (mean 144.48). A statistically significant difference between the groups was found in lung auscultation findings during the 3-month follow-up (supplemental table 4). A higher proportion of patients in the non-fibrotic-like group (90.28%) had normal lung sounds on auscultation compared to the fibrotic-like group (81.87%).

CT severity score

The mean CT severity score dropped from 12.19 on initial scans to 4.32 on follow-up scans (Table 2). The presented logistic regression model (Figure 5) examines how the CT Severity Score (CTSS) calculated on the initial scans influences the likelihood of developing fibrotic-like changes on follow-up CT scans at three months from discharge after COVID-19. CTSS serves as the indicator variable in the model, while the presence or absence of fibrotic-like changes is the dependent binary variable. The positive coefficient associated with the CTSS indicates a positive correlation between a higher initial CT severity score and a greater chance of experiencing fibrotic-like changes. Specifically, for every one-unit increase in the CTSS value (x), the odds ratio of having these changes increases by approximately 52,28%. The model

exhibits 80.10% accuracy in predicting the presence/absence of fibrotic-like changes, with 270 out of 337 observations aligning with the model’s predictions. The likelihood ratio (129.006) and its associated p-value (<0.001) are statistically significant at the alpha level of 0.05. In other words, the model suggests a positive association between a higher initial CT severity score and a greater statistical likelihood of developing fibrotic-like changes on control CT scans at three months.

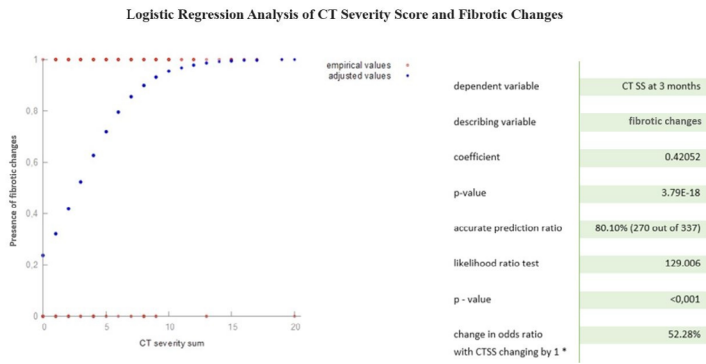


Figure 5: Logistic regression analysis of CT severity score and fibrotic changes.

Discussion

Previous outbreaks like SARS and MERS have shown a link between these infections and pulmonary fibrosis. Our study analyzed initial and three months post-discharge CT-scans of COVID-19 patients to identify potential risk factors for fibrotic lung changes. While a significant proportion of patients still presented lung abnormalities on follow-up CT scans, the severity of these abnormalities decreased considerably. This finding aligns with observations during the SARS-CoV-1 epidemic, where the prevalence of lung abnormalities also decreased over time [5,6]. Interestingly, vasodilatation was no longer detectable on follow-up scans. This finding aligns with our understanding of vasodilatation as a phenomenon primarily associated with acute inflammation. On the other hand, the study suggests a potential link between crazy paving and the development of fibrotic changes in the lungs. Although crazy paving can arise from various causes, it is also associated with ARDS, a known risk factor for lung fibrosis. In our study, patients with fibrotic-like changes were significantly older, had higher CT severity score at admission and demonstrated a higher rate of ICU admission during their initial hospitalization compared to those without these changes. This could imply that patients at risk of lung fibrosis had severe forms of disease or are somehow immunocompromised as elderly population. These findings are also suggested by other authors. E.g. Yu et al. also observed higher age and higher rate of admission to ICU as risk factors for fibrosis [7]. Lazar et al. identified significant associations between several factors at hospitalization and the presence of

fibrosis during follow-up [8]. These factors included inflammatory markers (CRP and ESR), LDH levels, hospitalization duration, antiviral treatment duration, and the extent of lung involvement (number of affected lobes, percentage of alveolar consolidation, mixed lesions, and interstitial lesions). These findings support our own observations where elevated inflammatory markers, specifically CRP and ferritin, were statistically associated with the presence of fibrotic-like changes in our study population. While mechanical and non-invasive ventilation are reported as potential risk factors for post-COVID fibrosis in some studies, e.g. from Li X, et al. [9], our investigation did not reveal a significant difference in the need for oxygen therapy between the groups with and without fibrotic-like changes. While some studies have reported a potential association between male gender and an increased risk of lung fibrosis following COVID-19 [10,11] our investigation did not identify a statistically significant difference in the prevalence of fibrotic-like changes based on gender. Early reports from discharged COVID-19 patients suggested smoking as a potential risk factor for the development of fibrosis, e.g. Marvisi, et al. [11]. However, our investigation did not observe a statistically significant correlation between smoking status and the presence of fibrotic-like changes.

One of the strengths of our study is a significant and representative sample and operating with standardized radiological assessment. We employed a regulated approach to radiological evaluation based on established guidelines such as the Fleischner Society: Glossary of Terms for Thoracic Imaging [12] and the glossary suggested by K. Martini, et al. [13]. This approach ensures consistency and reduces potential bias in the interpretation of CT scans. Our study has few limitations that warrant consideration when interpreting the findings. One of the limitations is lack of histopathological confirmation of fibrosis. Another important limitation is the follow-up period of three months after hospitalization. Longer-term studies are necessary to definitively determine if the observed fibrotic-like CT changes persist over time. Additionally, not all patients had a CT scan upon admission. Only patients who met the WHO-CPS criteria for moderate or severe COVID-19 were included in this analysis, which could introduce selection bias. We believe that our findings have potential clinical applications. The observed persistence of lung abnormalities on follow-up CT scans emphasizes the importance of post-discharge imaging for COVID-19 patients. The study findings might contribute to the development of strategies for identifying patients at higher risk of developing post-COVID fibrosis based on specific clinical or radiological characteristics.

Conclusion

In conclusion, this study demonstrates that older age, severe

initial illness requiring ICU admission and elevated inflammatory markers are important risk factors for developing fibrotic changes on follow-up CT scans after hospitalization for COVID-19.

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The Authors declares that there is no conflict of interest.

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